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Non-phenacetin analgesics and analgesic nephropathy

Clinical assessment of high users from a case-control study [1]*

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*This publication is dedicated to the memory of Professor Fokke J. van der Woude (1953–2006).

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Abstract

Background. A recent large-scale case-control study on analgesic nephropathy (SAN) [1] found no increased risk of end-stage renal disease (ESRD) in users of combined or single formulations of phenacetin-free analgesics. In a subgroup of 22 high users, however, a dose-dependent increased risk was found, which raised the question if these patients presented or not with analgesic nephropathy (AN).
Methods. The individual questionnaires of this subgroup of high users were reviewed, and the total lifetime intake of different types of analgesics was calculated. For evidence of AN, the following data were considered: (1) the amount and type of analgesics consumed, (2) the cause of ESRD, as diagnosed by the nephrologist in charge of the patient and (3) renal imaging and other relevant laboratory data.
Results. This group of ESRD patients consumed on average 7.8 kg of antipyretic analgesics (range 30.8–2.7 kg) over an average of 21.5 years (range 35–6 years). Single analgesics were exclusively used by 12 patients (54.5%) and combined analgesics by 5 patients (22.7%), while 5 patients used both. None of the patients was diagnosed as having AN, and a review of the questionnaires did not disclose evidence suggestive of AN. The possibility that, irrespective of AN, the analgesic (ab)use contributed to the progression of existing renal diseases cannot be answered in the absence of well-defined criteria. The data supporting the existence of such an analgesic-associated nephropathy (AAN) are, however, not consistent and most likely due to confounding by indication.
Conclusion. In a group of ESRD patients with high use of non-phenacetin analgesics, no evidence of AN was found. There is no evidence that (ab)use of analgesics or NSAIDs other than phenacetin leads to a pathologically or clinically defined renal disease that could be named AN or AAN.

Keywords: analgesic-associated nephropathy; analgesic nephropathy; combined analgesics; NSAID; phenacetin

Introduction

The nephrotoxicity of analgesics first came under attention by the observation of a large number of ESRD cases in patients abusing analgesic mixtures containing phenacetin. This new disease was named phenacetin nephropathy. The exclusive role of phenacetin as cause of analgesic nephropathy (AN) was later challenged, first by the group of Kincaid-Smith [2], later by De Broe and Elseviers [3,4]. This resulted in a redefinition of AN as 'a disease resulting from the habitual consumption over several years of a mixture containing at least two antipyretic analgesics and usually codeine or caffeine'. This new definition gained credibility after endorsement in 1996 by a Position Paper of the prestigious National Kidney Foundation [5]. Notwithstanding the questionable nature of the data supporting this new definition [6–9], it was accepted without restriction by leading nephrologists [10], which resulted in an official statement of the professional German-speaking associations of Nephrology at their 1996 Congress in Berlin [11]. The controversy persisted, however, mainly because of the difficulty in excluding the previous phenacetin intake [12,13]. This resulted in the setup of a large-scale case-control study in Germany and Austria [study on analgesic nephropathy (SAN)], its main objective being the control of such bias by including only patients younger than 50 years. The protocol of the study was published in detail [14], and in the recently published results [1] no evidence of an increased ESRD risk was found in users of combined or single formulations of phenacetin-free analgesics. In a subgroup of high users, however, a dose-dependent significantly increased risk of ESRD was found (Table 1). The present study was undertaken at the request of the SAN supervising Scientific Advisory Committee (SAC) to examine the clinical significance of this finding, and more specifically to determine if

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Table 1. Adjusted relative risk of ESRD by increasing cumulative lifetime dose of analgesic use at index date 3 (5 years before ESRD)[a]

Grams	Cases	Controls	OR (95% CI)
Low use	546	2030	1.00 (referent)
<500	278	1365	0.75 (0.64–0.88)
501–1000	41	133	1.10 (0.77–1.59)
1001–1500	10	47	0.76 (0.38–1.52)
1501–2000	6	19	1.03 (0.40–2.62)
2001–2500	4	9	1.50 (0.48–4.74)
2501–3000	3	8	1.35 (0.37–4.94)
≥3001	19	11	6.02 (2.83–12.81

[a]Data from the SAN study [1]. Reproduced with permission.

in this subgroup of high users ESRD was due to AN and related to heavy consumption of mixed antipyretic analgesics as defined in [5].

Methods

In the SAN study, all antipyretic analgesics, non-steroidal anti-inflammatory agents (NSAIDs) and additives such as caffeine and codeine are included in the calculation, and the consumption is calculated at different time intervals before ESRD. In order to minimize the risk of confounding by indication, the cumulative lifetime consumption until 5 years before admission for dialysis (index date 3) was selected for the final analysis. As shown in Table 1, the so-defined consumption exceeded 2500 g in 22 cases. As the present study is aimed at examining the evidence of AN in this subgroup of 22 high consumers, the analgesic intake was recalculated to bring it in line with the definition of classical AN [5,15]. The following criteria were applied:

1. The total lifetime intake of analgesics, until admission for dialysis (index date 1), was taken into account.
2. Only antipyretic analgesics (ASA, salicylates, aminophenazone, acetaminophen, etc.) were considered; NSAIDs such as diclofenac, ibuprofen, naproxen, etc. were not included.
3. Combined analgesics (Combi) were defined as the combination of at least two antipyretic analgesics.
4. The intake of caffeine, codeine and other additives was excluded from the calculation of the analgesic intake.
5. For total intake calculation, only the intake exceeding 6 months was considered. Occasional intakes for minor transitory discomforts were not included.

Criteria for diagnosis of AN

The questionnaires completed by the interviewers and the physicians responsible for the dialysis of these 22 cases were further reviewed for evidence of AN by one of the authors (P.M.). As no autopsy data were available on these 22 cases, the diagnosis of AN was evaluated on the following data.

1. The cause of the ESRD, as estimated by the physician in charge of the patient.

Table 2. Number of patients in each category of analgesic consumption, calculated at index 3 (5 years before ESRD), and at index 1 (at admission for dialysis)

Grams	All analgesics[a] index 3	All analgesics[b] index 1	Antipyretic analgesics[b] index 1
2501–3000	3	0	2
3001–3500	5	2	1
3501–4000	2	4	3
4001–5000	4	3	3
5001–6000	2	0	1
>6000	6	13	12

[a]Data from the SAN study [1].
[b]Data obtained from the questionnaires.

2. Imaging data compatible with papillary necrosis [16].
3. Detailed history of past (ab)use of antipyretic analgesics.

Results

Analgesic intake

As shown in Table 2, the inclusion in the calculation of the last 5 years before ESRD markedly increased the estimated lifetime consumption, but the strict restriction to antipyretic analgesics had only a marginal effect.

The lifetime consumption of antipyretic analgesics by these 22 cases averaged 7.8 kg (range 30.8–2.7), which is within the range of abuse reported as having induced AN. In Table 3, the patients/cases are separated in three groups according to the type of antipyretic analgesics consumed: only five patients had used exclusively combination formulations (Group I) and their average intake was 12.6 kg (range 30.8–2.7). Another five patients had used both single and combination formulations (Group II), with an average intake of 5.4 kg (range 7.5–4.1). Single preparations were used by 12 cases (Group III) and their average intake was 6.8 kg (range 19.2–2.9). NSAIDs were taken by seven patients: mefenamic acid by patients Id, Ie, IIc; ibuprofen by patients IIb, IIIa, IIId; diclofenac by patient IIIe (data not shown).

The compulsive daily intake of a large number of tablets over a prolonged period of time is a characteristic of phenacetin abuse [17]. In our patients, a continuous daily intake during 1 year or more was only found in three users of combined analgesics and eight users of single analgesics and the daily intake of tablets was much lower than reported for phenacetin-containing Combis (Table 3).

Diagnosis of AN

For a study aimed at evaluating the causal nature of a relationship between high intake of combined analgesics and AN, an unequivocal definition of AN and reliable criteria of diagnosis are essential. Based on autopsy observations in patients abusing phenacetin-containing mixed analgesics, AN was defined as characterized by papillary necrosis and secondary parenchymal lesions. This papillary necrosis is linked to the presence of capillary sclerosis, a specific

Table 3. Lifetime antipyretic analgesic consumption for users of Combi(I), mono(III) or both (II)

		Antipyretic analgesics							
		Combinations				Single products			
Cases	Diagnosis	Gram	Tablets/day	Days/year	Years	Gram	Tablets/day	Days/year	Years
Ia	Unclear	30 812	6	365	32				
Ib	Polycystic kidneys	12 318	15	365	6				
Ic	Unclear	10 767	8	365	11				
Id	Polycystic kidneys	6 464	3	144	34				
Ie	Unclear	2 658	3–4	12–30	15				
IIa	Diabetic nephropathy	803	3–4	72–208	7	6 721	2–10	156–208	24
IIb	Diabetic nephropathy	5 254	4	108	24	875	3	25	24
IIc	Unclear	234	2	10	28	4 858	3	10–56	35
IId	Focal glomerulosclerosis	1 002	4	24	24	3 080	4	48	26
IIe	Diabetic nephropathy	1 390	2	12–30	30	2 684	2	12–90	30
IIIa	Diabetic nephropathy					19 208	1–10	14–365	16
IIIb	Unclear					14 933	2–10	6–365	14
IIIc	Diabetic nephropathy					6 879	2–3	7–365	28
IIId	Polycystic kidneys					6 547	2	365	19
IIIe	Diabetic nephropathy					6 436	2–3	42–365	25
IIIf	IgA nephropathy					6 193	4–2	365	20
IIIg	Lupus nephritis					4 668	2–4	36–104	19
IIIh	Diabetic nephropathy					3 689	1–3	24–365	30
IIIi	Amyloidosis					3 628	2	156	25
IIIj	Malignant hypertension					3 503	3–4	182	17
IIIk	Glomerulonephritis					3 380	3	365	7
IIIl	Renal infarction					2 870	2	4–147	20

Cause of ESRD as reported in the medical questionnaire.

lesion of the capillaries in the papillae and the mucosa of the pyelon and ureter. In the clinical setting, as substitute for a pathological diagnosis, a CT scan finding of bilaterally decreased renal mass combined with bumpy contours and, in particular, papillary calcifications became accepted as diagnostic of AN [18,19]. Such renal lesions have been claimed to result from the abuse of combined analgesics with or without phenacetin [5,15,16].

The diseases considered responsible for ESRD are mentioned in Table 3. In 17 patients a clear diagnosis is indicated, consistent with the progression to ESRD; for five cases the diagnosis was reported as unclear, but none of the patients was diagnosed as presenting AN. In addition to diabetic nephropathy, which was reported as responsible for ESRD, patient IIIe had undergone a right nephrectomy for nephrolithiasis and pyonephrosis. In the absence of computer tomography, available echography data were reviewed for evidence suggesting papillary necrosis. None of the patients presented small indented kidneys with papillary calcifications (Table 4).

The clinical data of the cases with unclear diagnosis were as follows:

Case Ia is a 44-year-old woman who had taken combined analgesics for more than 30 years. She was a regular heroin and cocaine user for 25 years. The association of proteinuria >2 g/24 h, a rapidly progressing renal failure and a biopsy finding of extreme tubular atrophy with interstitial fibrosis may be suggestive of 'heroin nephropathy'. Echography did not suggest AN.

Case Ic is a 46-year-old woman who started taking combined analgesics at age 35 for prevention of headache. There are inconsistencies in the medical history as reported in the questionnaire. Objective data are scarce. Proteinuria is indicated as positive but without mentioning the degree. Echography disclosed small bumpy kidneys without calcifications. The following ESRD risk factors were present: hypertension, obesity (BMI 33), heavy smoker since age 17. The available data are insufficient to eliminate or confirm a diagnosis of AN.

Case Ie is a 42-year-old patient with a long-standing history of kidneys reduced in size, proteinuria, hypertension and toxaemia of pregnancy. There are no reasons to suspect AN. This patient also consumed 799 g of mefenamic acid over 26 years.

Case IIc is a 47-year-old woman with a long-term history of intermittent use of various analgesics. She presented hypertension and proteinuria >2 g/24 h. There are no reasons to suspect AN. This patient consumed 1032 g of mefenamic acid over 24 years.

Case IIIb is a 44-year-old man with insulin-dependent diabetes mellitus since the age of 3 years. He had a heart transplant and was suspected of cyclosporine toxicity.

Discussion

The data from the study questionnaires are unequivocal: In that none of the 22 patients in this group of high analgesic users was AN diagnosed by the referring nephrologists.

Table 4. Clinical characteristics and risk factors for ESRD

Case	Sex	Intake of antipyretic analgesics (g)	Proteinuria		Echography			Hypertension	Body mass index	Smoking		
			<2 g	>2 g	Reduced size	Bumpy contour	Papillary calcifications			Ever	Still smoking	Packs/year
Ia	F	30 812		Positive	+	−	−	+	23.14	Yes	Yes	60
Ib	F	12 318	Negative		−	−	−	+	26.26	Yes	Yes	15.5
Ic	F	10 767	+?	+?	+	+	−	+	33.02	Yes	Yes	28
Id	M	6 464	Not available		−	−	−	+	22.63			
Ie	F	2 658	Positive		+	−	−	+	22.28	Yes		13.5
IIa	M	7 524	Positive		−	+	−	+	22.41			
IIb	F	6 129	Not available		−	−	−	−	33.95	Yes		4.5
IIc	F	5 092		Positive	+	−	−	+	25.22	Yes		0.25
IId	M	4 082		Positive	−	−	−	+	21.43	Yes	Yes	18.75
IIe	M	4 074		Positive	+	−	+	+	19.34	Yes	Yes	18
IIIa	M	19 208		Positive	Not available			+	23.29	Yes	Yes	33
IIIb	M	14 933	Not available		Not available			+	23.37	Yes	Yes	20
IIIc	M	6 879	Positive		−	−	−	+	28.58	Yes		57.5
IIId	M	6 547	Negative		−	−	−	+	25.93			
IIIe	F	6 436	Positive		−	−	−	+	31.20			
IIIf	M	6 193	Positive		+	−	−	+	36.59			
IIIg	F	4 668		Positive	+	−	−	+	23.34			
IIIh	M	3 689	Positive		−	−	−	+	29.63	Yes		18
IIIi	F	3 628	Not available		+	−	−	+	14.82			
IIIj	M	3 503	Positive		+	−	−	+	24.49	Yes	Yes	11
IIIk	M	3 380		Positive	+	−	−	+	30.78			
IIIl	M	2 870	Negative		−	−	−	+	32.41	Yes		14

Data from the questionnaires.

Has the diagnosis of AN been missed? Without autopsy and without a CT scan this cannot be excluded, but in most patients there was clear evidence of another diagnosis, and in the patients with unclear diagnosis there was no evidence of papillary necrosis. A missed diagnosis of AN is unlikely for the following additional reasons:

- It is true that a clinical diagnosis of AN can be difficult, but in most studies claiming the toxicity of combined analgesics, the diagnosis of AN was also a clinical diagnosis. It is unlikely that the nephrologists in charge of the patients would have lost their diagnostic skills, especially in Germany and Austria, countries with a high degree of awareness of AN among both the medical profession and the public.
- Analgesic intake did not correspond to the pattern deemed responsible for AN.
- In ESRD patients without clear diagnosis, a recent large-scale epidemiological study concluded that CT findings similar to those described by De Broe [18] were present only in a minority of heavy analgesic users [20], particularly when phenacetin intake was excluded. The data from the present study are consistent with this conclusion.
- Also consistent with our study are the results of a population-wide case-control study in Sweden [21]. In this study, AN nephropathy as described by Elseviers and De Broe [18] was not found in patients with newly diagnosed renal failure.
- At the request of the SAN supervising scientific committee, Mihatsch conducted in 2006 an exact replication of his autopsy study performed in 1978–1980 in Basel [22]. The conclusion of this new study was that AN had disappeared [23]. It is unlikely that AN would have disappeared in Basel, but not in Germany and Austria.

Altogether, these arguments lead to the conclusion that the diagnosis of the referring physicians can be assumed to be correct and that the dose-dependent correlation found in the SAN study between high analgesic intake and ESRD was not due to AN. This, however, raises the question of the *adequacy of the design of the SAN study*. The title of the SAN study [1] suggests that it is only relevant to young age, as previous phenacetin (ab)use was eliminated by setting the age limit at 50 years. Did this age limit preclude the necessary massive consumption of analgesics and/or was the duration of observation sufficient to develop AN?

In most studies the cut-off point, defining the cumulative intake of analgesics correlated with an increased risk of AN, is 1 kg or 5000 pills lifetime use [19]. In the subgroup of high users investigated in the present study, the lowest lifetime intake was 3 kg, the maximum 30 kg and the duration of abuse varied between 6 and 32 years. The age limit of 50 years was obviously more than adequate to allow for the massive consumption of analgesics reported as having caused AN.

The second question concerns the delay needed for the development of AN. In the definition of AN as a consequence of abuse of unspecified mixed antipyretic analgesics, it is assumed that the earlier observed phenacetin toxicity was only part of a broader toxicity involving all mixed antipyretic analgesics. If this hypothesis were correct, the massive use of combined analgesics could be expected to induce the same lesions within the same time limit as if these combined analgesics contained phenacetin. As long as phenacetin-containing analgesics were still used, AN was a disease of middle age. Autopsy data from Basel [24] indicate that in the years 1948–1957, the maximal increase in the number of cases of chronic interstitial nephritis occurred in the age group of 31–40 years. Australian data published in 1970 [2] indicate that more than half of the patients with AN were below 50 years of age. The obvious explanation for the present-day finding of AN as a disease of older age is that these cases, as seen today, are only late consequences of previous phenacetin abuse. This is consistent with the parallel modification of the autopsy findings. As described by Mihatsch, the normal sized kidneys shedding necrotic papillae, routinely found at autopsy in the sixties, evolved progressively to the present-day finding of small bumped kidneys with papillary calcifications [25,26].

It can be concluded that the relevance of the SAN study was not limited to younger age and that it was adequate to detect AN if it had occurred. Taken together with the disappearance of AN from the autopsy studies in Basel, the present study leads to the inescapable conclusion that AN has disappeared with the ban of phenacetin and is no longer a public health problem. The term AN was introduced to include unspecified antipyretic analgesics or a combination thereof as causal factors. As there is no evidence to support this extension, AN should be renamed ‘phenacetin nephropathy’.

In the SAN study, as in most epidemiological studies on the nephrotoxic role of analgesics, the end-point is not AN but ESRD. In the absence of validation of evidence of AN, the term ‘analgesic-associated nephropathy’ (AAN) is used in most of these studies and, besides AN, a contribution to the progression of existing renal diseases has been considered as possible. This possibility was most often considered for acetaminophen [21,27,28], but was not confirmed in other studies [1,29]. However, as acetaminophen is recommended as the analgesic of choice in patients with renal disease [5], there is an increased risk of confounding by indication. The inconsistency of the data and the risk of bias have led to consider the evidence as inconclusive in several reviews [15,30,31].

The inconsistency of the data when individual analgesics are considered has led to a further enlargement of the definition of AAN, including not only single or combined analgesics but also NSAIDs as contributing to the development or the progression of chronic renal disease of whatever aetiology [19]. All analgesics and NSAIDs are inhibitors of cyclooxygenase (COX), and it is tacitly assumed that they could therefore share the same toxicity for the kidney. It is beyond doubt that all analgesics could influence renal function. However, using COX inhibition as a common link to consider together different analgesic drugs, ignores that there are different COXs and that the selectivity and activity of the inhibition differ from drug to drug (review in [32]). Furthermore, COX inhibition can have positive as well as negative aspects. For the evaluation of the

possible effects of COX inhibition on existing renal diseases, different influences should be considered.

1. *The influence on homeostasis*: five different prostaglandins play a major role in the regulation of various aspects of renal function [33]. In the presence of reduced renal perfusion, especially in the elderly, COX-2 inhibition can lead to acute renal failure. The risk will be dependent on the inhibition ratio COX-2/COX-1 for the drug considered. As salicylic acid and acetyl salicylic acid are highly selective for COX-1, their influence on renal homeostasis will be negligible. Similarly, acetaminophen does not significantly inhibit either COX-1 or COX-2 but mainly COX-3, which is only present in the brain [32]. This influence on the homeostasis is drug specific and not common to all COX inhibitors. It is, however, not always negative as illustrated by the control of Bartter's syndrome by indomethacin administration [34].
2. *The influence on pathological processes*: Up-regul-ation of the expression of COX-1 and COX-2 is a response of the kidney to various aggressions, and especially COX-2 expression is increased in the macula densa and in some glomerular structures [35]. Influence of cyclooxygenase inhibitors can therefore be expected. One of the first reported examples of such an influence is the decrease of proteinuria under treatment with indomethacin [36,37]. This reduction is not only related to a reduction of the glomerular filtration but also to a restoration of the size-selectivity barrier [38]. These earlier clinical observations are now supported by consistent experimental data [35,39–45]. In contrast with the majority of these experiments showing an improvement in the renal injury, COX-2 inhibition increased proteinuria and interfered with the healing process in a model of spontaneously recovering glomerulonephritis induced by anti-Thy1.1 [46].

Analgesics can also induce drug-specific adverse effects, unrelated to COX inhibition. Occasional hypersensitivity and interstitial nephritis can also occur in antipyretic analgesics as a drug-specific complication. Some NSAIDs, mainly fenoprofen, can in rare cases induce a nephrotic syndrome with a typical pathological picture of interstitial nephritis [47]. If these specific diseases occur superimposed on existing renal diseases, they could influence the progression to ESRD, without loosing their identity. Bringing these specific diseases together with AN under the non-specific common name of AAN could only result in confusion.

In summary, the simplistic hypothesis of a contribution to the progression of existing renal diseases, common to all analgesics or NSAIDs, does not fit in with the clinical and experimental data. The influence of Cox inhibitors on the progression of existing renal diseases is a complex process with positive and negative aspects, without a common pathological or clinical definition. In the absence of well-defined criteria, the SAN study as well as the earlier epidemiologic studies does not provide convincing evidence justifying overstretching the concept AN to include all possible negative effects of analgesics and NSAIDs, and consequently the concept of AAN should be reconsidered.

Conclusion

The present study failed to find evidence that AN was the cause of ESRD in the group of high users of single or combined analgesics reported in the SAN study. These findings support the conclusion [23] that AN should be renamed phenacetin nephropathy. Furthermore, there is no sound theoretical or clinical justification for maintaining the name AAN for an entity including, besides phenacetin nephropathy, a contribution by single or combined analgesics and NSAIDs to the development or the progression of chronic renal disease of whatever aetiology.

Acknowledgements. Table 1 is reproduced from reference [1] under the terms of Biomed Central's Open Access Charter. The authors are indebted to Karin Thiele for review and correction of the paper.

The present study is based on data from a case-control study on analgesics and nephropathy (SAN) [1], details of which can also be found on the SAN website: http://www.san-study.com. The SAN study was initiated at the initiative of the German regulating authorities (BfArM); it was scientifically independent, sponsored by the industries and governed by an international Scientific Advisory Committee (SAC). The present study is an individual evaluation of a subgroup of high consumers, performed by P.M. at the request of the German Drug Authority and the SAC.

Conflict of interest statement. The results presented in this paper have not been published previously in whole or part in a peer-reviewed journal. A summary of the results has been published in [1]. L.H. was the Epidemiological Principal Investigator and H.G was the Clinical Principal Investigator of the SAN study. K-M.K. was the chairman, and P.M., M.M. and P.S. were members of the SAC. None of the authors declared a conflict of interest.

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